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SPECIAL REPORT

Short-term efficacy and safety of early medical abortion in Japan: A multicenter prospective study

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Abstract

Purpose: To evaluate the short-term efficacy and safety of a combined mifepristone-misoprostol regimen in individuals seeking medical abortion at up to 63 days of gestational age.

Methods: This open-label, multicenter, prospective study evaluated the short-term efficacy and safety of medical abortion, with the primary outcome being the abortion success rate 24 h after misoprostol administration. The participants received 200 mg of mifepristone orally and 800 μg of misoprostol buccally in the hospital/clinic 36–48 h later. Bleeding and lower abdominal pain, which are the main symptoms associated with medical abortion, were recorded.

Results: The abortion success rate was 93.3% (95% confidence interval [CI]: 87.3–97.1%) within 24 h of misoprostol administration, 63.3% (95% CI: 54.05–71.94%) within 4 h, and 90.0% (95% CI: 83.18–94.73%) within 8 h. The median time from misoprostol administration to a successful abortion was 3.93 h. Bleeding was most commonly observed 0–4 h prior to the confirmation of gestational sac (GS) expulsion. The most intense lower abdominal pain occurred 0–1 h before the confirmation of GS expulsion.

Conclusion: The combined regimen of mifepristone and buccal misoprostol for medical abortion showed short-term efficacy and a favorable safety profile.

KEYWORDS
abortion, combination therapy, Japan, mifepristone, misoprostol

1 | INTRODUCTION

Medical abortion plays an essential role in the provision of access to safe, effective, and well-accepted abortion care; mifepristone and misoprostol are globally available and part of the World Health Organization (WHO)'s model list of essential medicines.[1] Treatment regimen involves an initial dose of mifepristone, followed by misoprostol, a synthetic prostaglandin analog that induces cervical softening and dilation and enhances uterine contractions, aiding in expulsion of the products of conception.[2,3]

The combined use of mifepristone and misoprostol for the artificial termination of early pregnancy offers several advantages, including the reduction of the need for surgical abortion, and provides a noninvasive and highly acceptable option for pregnant individuals.[4]

Clinical Trial Registration: Registry Name: JAPIC Clinical Trials Information (former registry platform of JCRT). URL: https://www.clinicaltrials.jp/cti-user/trial/List.jsp. Registration number: JapicCTI-195008. Date of enrollment: 2019/10/31.

A regimen of 200 mg of mifepristone followed by the administration of misoprostol is indicated for early medical abortion worldwide. In particular, the WHO recommends the administration of 200 mg of mifepristone, followed by administration of 800 μg of buccal misoprostol 1–2 days later.[5]

In Japan, surgical abortion is currently the only permissible method for the artificial termination of early pregnancy. In the present study, we assessed the efficacy and safety of medical abortion not only to obtain authorization for the WHO-recommended regimen for early medical abortion in order to fulfill the unmet medical needs in Japan but also to provide relevant additional information on the short-term efficacy and safety profile of this procedure. Hence, the present study aimed to demonstrate the 24-h efficacy of a combined regimen of 200 mg of oral mifepristone followed by 800 μg of buccal misoprostol in Japanese individuals seeking artificial termination of pregnancy up to 63 days of gestational age.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

This phase III, open-label, multicenter, prospective study recruited a total of 123 participants across 18 sites in Japan between November 11, 2019, and March 31, 2020. This study was conducted in accordance with the principles set forth in the Declaration of Helsinki and Japanese Good Clinical Practice. Furthermore, this study was reviewed and approved by the Institutional Review Board and informed consent was obtained from all participants. The study was registered at the JAPIC Clinical Trials Information (registration number: JapicCTI-195008). Because this was the first study in Japan to evaluate medical termination of early pregnancy, the participants were hospitalized throughout the treatment period to ensure their safety and to evaluate the short-term efficacy and safety of the regimen. The hospitalization period was from days 1 to 15, and the participants were discharged upon confirmation of gestational sac (GS) expulsion.

2.2 | Study population

The inclusion criteria for the recruited women were as follows: (1) 18–45 years of age at screening visits; (2) seeking medical abortion; (3) having normal intrauterine pregnancies of up to 63 days at mifepristone administration; (4) exhibiting clinical and biological status appropriateness for medical abortion; and (5) expressing willingness to undergo surgical abortion, if needed.

The exclusion criteria for this study were as follows: (1) suspected/diagnosed ectopic pregnancy or undiagnosed adnexal mass; (2) presence of an intrauterine device; (3) known allergies to mifepristone, misoprostol, or any other prostaglandin; (4) having chronic kidney disease, adrenal insufficiency, steroid-dependent conditions including asthma, coagulopathies, or hereditary porphyria; (5) long-term treatment with corticosteroids or ongoing treatment with anticoagulants; and (6) any medical condition that, in the judgment of investigators, would impair participation in the study.

2.3 | Treatments

The participants were screened for eligibility following the acquisition of their written consent. Eligible participants were administered 200 mg of oral mifepristone (Mifepristone Linepharma®, Linepharma International Limited, London, UK) followed by 800 μg of buccal misoprostol (200 μg tablet ×4 tablets via single dose; GyMiso®, Linepharma International Limited, London, UK) 36–48 h after mifepristone administration.

2.4 | Monitoring

Using the modified Pictorial Blood Loss Assessment Chart (PBAC), all participants tracked bleeding after mifepristone administration every 2–3 h (every 4–6 h after discharge) except when sleeping, and whenever they changed pads.[6] Additionally, the participants recorded the severity of lower abdominal pain at the same intervals using an 11-point numeric rating scale (NRS). Medications for pain were also recorded.

Adverse events (AEs), including those of special interest such as bleeding, infection, nausea, vomiting, and lower abdominal pain, were recorded throughout the study. Investigators checked for ongoing pregnancies every 4 h or whenever requested. Medical termination of pregnancy was deemed complete when GS expulsion was confirmed by transvaginal ultrasonography. Retained products were considered acceptable, provided that they were not associated with prolonged/heavy bleeding or persistent fever.

Successful abortion was assessed 24 h after misoprostol administration. The participants who did not experience a complete abortion 24 h after misoprostol administration could stay in the hospital or clinic up to 14 days after mifepristone administration or could request a surgical abortion any time after the primary outcome assessment. Follow-up visits were conducted 7 days after discharge.

2.5 | Outcomes

The primary outcome was the abortion success rate from mifepristone administration up to 24 h after misoprostol administration. The key secondary efficacy outcomes were as follows: (1) abortion success rate from misoprostol administration up to 24 h after misoprostol administration; (2) abortion success rate every 4 h after misoprostol administration; and (3) time to abortion from mifepristone administration and from misoprostol administration.

2.6 | Sample-size calculation and statistical analyses

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were expressed as the number, mean with standard deviation (SD), minimum, median, and maximum for continuous variables and as the number and percentage of individuals for categorical variables.

An efficacy analysis with two-sided 95% confidence intervals (CIs) was conducted using a full analysis set and a per-protocol analysis set. The primary analysis was done on the full analysis set. For the primary efficacy outcome (the proportion of participants with successful abortion confirmed between mifepristone administration and 24 h after misoprostol administration), the 95% CI was calculated using an exact test. The efficacy was confirmed when the lower limit of 95% CI for the efficacy rate exceeded 0.50. Subgroup analyses were performed on the primary outcome with respect to the participants' clinical and obstetrical profile: age, gestational age, parity, and induced abortion history. The time to abortion from mifepristone administration and from misoprostol administration was analyzed using the Kaplan–Meier method.

The type, frequency, severity, and seriousness of AEs throughout the study period were reported. All AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. The modified PBAC and NRS scores were summarized using descriptive statistics at each time interval.

Assuming that the success rate of pregnancy termination within 24 h after misoprostol administration would be 65.0%,[7] a sample size of 120 participants was determined to be required using a two-sided exact test at a 5% significance level with 90% power, considering a withdrawal rate of 5%. The efficacy threshold was set at 50%.

3 | RESULTS

A total of 120 participants who were eligible according to the inclusion/exclusion criteria were enrolled in the study and received the investigational medical product (IMP). Four participants discontinued after the primary outcome evaluation owing to request surgical abortion. Hence, a total of 116 participants completed the study. No major protocol deviations were observed in any participant (Figure 1).

All participants were Asian, with a mean (±SD) age of 28.1 ± 6.8 years, and 40.0% (n = 48) were aged over 30 years. The average gestational age at the time of the first IMP administration was 51.7 ± 6.6 days of gestation, and 59.2% (n = 71) had gestational age ≥50 days (Table 1).

A total of 112 participants (93.3%; 95% CI: 87.3–97.1%) had a successful medical abortion confirmed between mifepristone administration and 24 h after misoprostol administration, without additional surgical procedure (primary outcome) (Table 2). Overall, 95.8% (n = 115) of participants experienced spontaneous medical abortion at 24 h after misoprostol administration (Figure 1). Despite spontaneous medical abortion occurring within the first 24 h of misoprostol administration, an additional surgical procedure was needed in three participants. Additionally, another participant needed a surgical procedure after medical abortion occurred approximately 48 h after misoprostol administration. Four participants with ongoing pregnancies requested surgical procedures between 24.6 h and 26.3 h after misoprostol administration and were subsequently withdrawn from the study (Figure 1).

In 108 out of the 120 participants, abortion occurred between mifepristone administration and up to 8 h after misoprostol administration, with the cumulative success rate being 90.0%. Two abortions

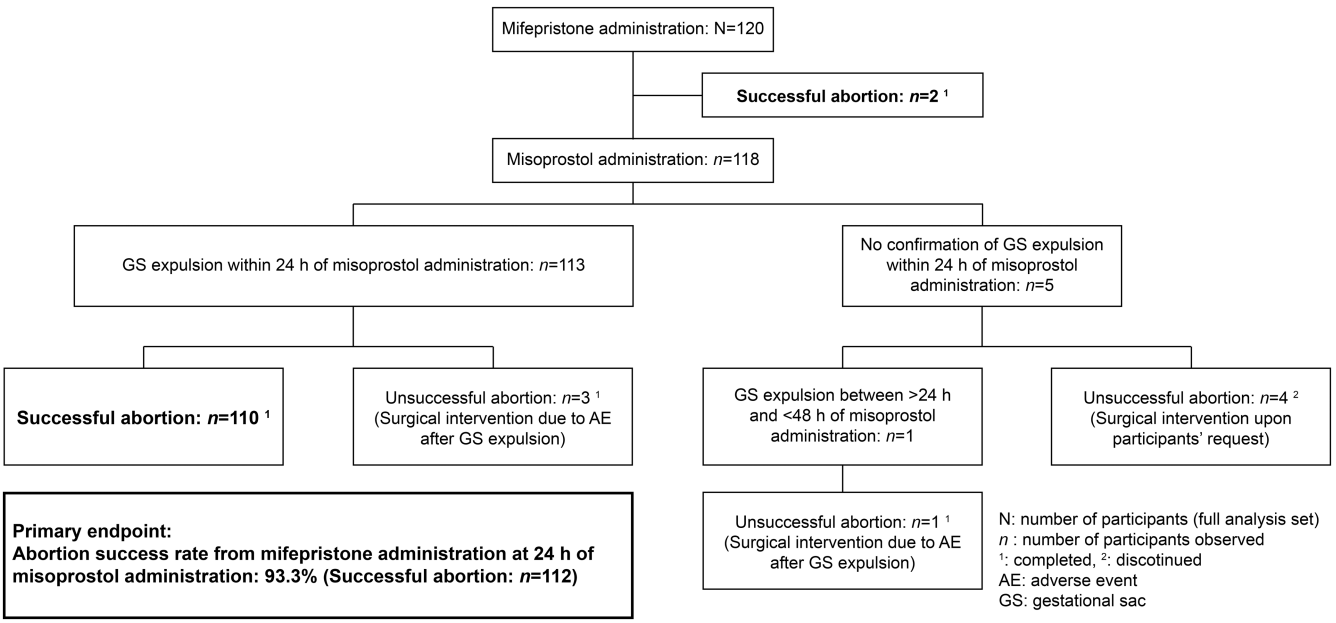


FIGURE 1 Disposition of participants. The diagram shows disposition of participants in this study, including number of participants with successful abortion or unsuccessful abortion, and reasons for unsuccessful abortion.

occurred prior to misoprostol administration. When analyzed every 4 h after misoprostol administration, the success rate was 61.7% ($n = 74$) within the first 4 h and 26.7% ($n = 32$) between 4 and 8 h after misoprostol administration (Figure 2). The median time from mifepristone administration to a successful abortion was 48.03 h (95% CI: 47.50–48.60, $n = 120$), whereas the median time from misoprostol administration to a successful abortion was 3.93 h (95% CI: 3.40–4.35, $n = 118$) (Table 3). The success rate of medical abortion within 360 h after mifepristone administration was 93.8% (95% CI: 86.8–97.1%) based on the Kaplan–Meier estimate (Figure 3).

With respect to the success rate of medical abortion according to the participants' clinical and obstetrical profile, the success rate was above 90%, irrespective of the participants' age (94.4% [95% CI: 86.4–98.5%] vs. 91.7% [95% CI: 80.0–97.7%]). Participants with a gestational age of <42 days showed a lower success rate of 83.3% (95% CI: 51.6–97.9%), whereas the other groups achieved success rates comparable to the rate observed across the entire study population. Parity and previous history of induced abortion did not appear to affect the success rate 24 h after misoprostol administration (Table 4).

Overall, 69 (57.5%) participants reported at least one AE. The majority of AEs were mild or moderate; however, three (2.5%) participants developed severe AEs (Table 5). Furthermore, four (3.3%) participants experienced serious AEs during the treatment phase, none of which led to death or trial discontinuation. An additional serious AE of "abortion induced incomplete" was reported in one participant during the post-treatment phase (Table 6). The AEs reported by 45 (37.5%) participants were judged to be possibly related to the IMPs, which were considered adverse drug reactions (ADRs); the most frequently reported ADRs were lower abdominal pain (15.0%) and diarrhea (14.2%). One (0.8%) participant experienced serious ADRs (blood loss anemia and "abortion induced incomplete"), and another one (0.8%) participant reported a severe ADR (lower abdominal pain) (Table 7).

As expected, all participants experienced bleeding, commencing after mifepristone administration in 73 participants (60.8%) and after misoprostol administration in 47 participants (39.2%). The average duration was 614.9 ± 392.8 h (range: 139–2392 h). The modified PBAC score was the highest 0–4 h before confirmation of GS expulsion and then 0–4 h after confirmation of GS expulsion; the modified PBAC score gradually decreased thereafter (Figure 4).

TABLE 1 Demographic characteristics of the study population enrolled in the study ($N = 120$).

Age, years (mean ± SD)	**28.1 ± 6.8**
Ethnicity, *n* (%)	
Asian	120 (100.0)
Others	0 (0.0)
Height, cm (mean ± SD)	157.9 ± 5.1
Weight, kg (mean ± SD)	53.3 ± 8.5
BMI, kg/m^2 (mean ± SD)	21.4 ± 3.4
Gestational age, days (mean ± SD)	51.7 ± 6.6
Parity, *n* (%)	
Nulliparous	63 (52.5)
Multiparous	57 (47.5)
History of induced abortion	
Yes	33 (27.5)
No	87 (72.5)
Intensity of menstrual cramps	
None	19 (15.8)
Mild	59 (49.2)
Moderate	32 (26.7)
Severe	10 (8.3)

Note: Results are presented as the mean ± SD or percentage (%).
Abbreviations: *N*, number of participants (full analysis set); *n*, number of participants observed, %, percentage of participants.

TABLE 2 Summary of success rate (full analysis set).

Success rate	***N***	***n***	**Rate (%)**	**95% CI (%)**
Primary outcome				
Success rate between mifepristone administration and within 24 h after misoprostol administration	120	112	93.3	87.3–97.1 (Clopper-Pearson exact test)
Secondary outcomes				
Success rate between misoprostol administration and within 24 h after misoprostol administration	118[a]	110	93.2	87.1–97.0 (Clopper–Pearson exact test)
Success rate between mifepristone administration and within 4 h after misoprostol administration	120	76[b]	63.3	54.1–71.9 (Clopper–Pearson exact test)
Success rate between mifepristone administration and within 8 h after misoprostol administration	120	108[b]	90.0	83.2–94.7 (Clopper–Pearson exact test)

Note: The intention-to-treat (ITT) analysis set included all participants who signed an informed consent form and were registered for the study. The full analysis set consisted of ITT participants who took an investigational medical product (IMP) and had evaluable efficacy data after baseline.
Abbreviations: *N*, number of participants (full analysis set); *n*, number of participants with successful pregnancy termination.
[a]The number of participants who received misoprostol in the full analysis set (full analysis set less 2 participants who did not receive misoprostol).
[b]Two abortions that occurred before misoprostol administration were included.

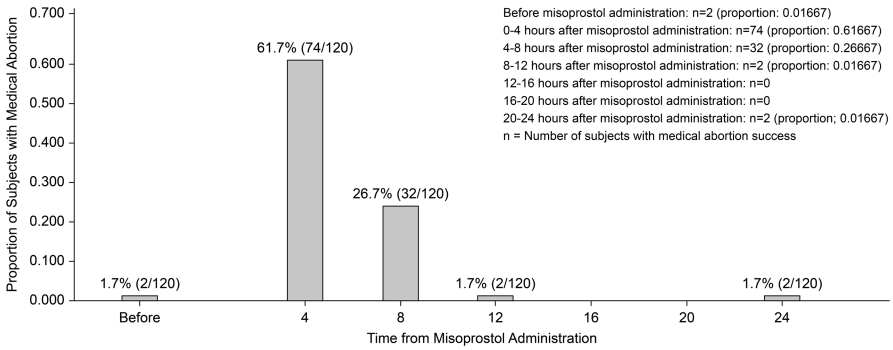
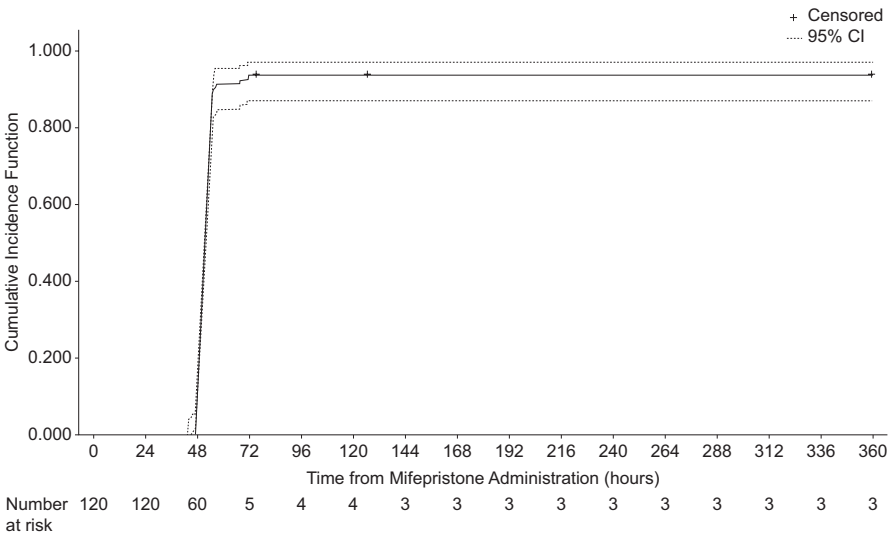


FIGURE 2 Success rate at each timepoint with 4-h increment after misoprostol administration. The success rate was 61.7% within the first 4 h and 26.7% between 4 and 8 h after misoprostol administration.

TABLE 3 Time to successful abortion using the Kaplan–Meier method (full analysis set).

Time to successful abortion (hours)	*N*	Quartile	Estimates	95% CI
Time from mifepristone administration to successful abortion	120	Median	48.03	47.50–48.60
Time from misoprostol administration to successful abortion	118	Median	3.93	3.40–4.35

Abbreviation: *N*, number of participants (full analysis set).



Time from Mifepristone Administration (hours)	Number at risk	Censored	Cumulative Incidence	95% CI
0.00	120	-	0.000	-
39.40	120	No	0.008	0.001 - 0.042
48.07	60	No	0.525	0.431 - 0.610
72.33	5	Yes	0.938	0.868 - 0.971
125.07	4	Yes	0.938	0.868 - 0.971
360.00	3	Yes	0.938	0.868 - 0.971

According to the protocol, those who required surgical intervention after confirmation of gestational sac expulsion were treated as Censored at the time of surgical intervention.

FIGURE 3 Cumulative incidence for the time to medical abortion from mifepristone administration. The success rate of medical abortion within 360 h after mifepristone administration was 93.8% (95% CI: 86.8–97.1%) based on the Kaplan–Meier estimate.

When lower abdominal pain was analyzed using the NRS, the mean (±SD) maximum score from mifepristone administration to discharge was 5.2 ± 3.00 (range: 0–10, $n = 120$). The most intense lower abdominal pain occurred 0–1 h before confirmation of GS expulsion and then persisted at a consistent level until 3–4 h after confirmation of GS expulsion (Figure 5).

4 | DISCUSSION

This study is the first report on the early outcomes of artificial pregnancy termination using the combined regimen recommended by the WHO (200 mg of oral mifepristone +800 μg of buccal misoprostol).[5] Of the 120 participants in the present study, 93.3% had successful abortion within 24 h after misoprostol administration (63.3% within 4 h and 90.0% within 8 h).

Previous reports in the literature had indicated the regimen's efficacy rates ranged from 86.5% to 100%, 10–14 days after misoprostol administration.[6–14] It should be noted that the success rate 24 h after misoprostol administration observed in our study was similar, proving that this regimen is a quick and efficient procedure for early abortion.

Only one previous study monitored the timing of GS expulsion after individuals received 600 mg of mifepristone and 400 μg of

TABLE 4 Proportion of participants with successful abortion from mifepristone administration to 24 h after misoprostol administration according to the clinical and obstetrical profile (full analysis set).

Subgroups		*N*	Percentage	95% CI
Age (years)	≤29	72	94.4	86.4–98.5
	≥30	48	91.7	80.0–97.7
Gestational age (days)	≤42	12	83.3	51.6–97.9
	43–49	37	94.6	81.8–99.3
	50–56	39	94.9	82.7–99.4
	57–63	32	93.8	79.2–99.2
Gestational age (days)	≤49	49	91.8	80.4–97.7
	≥50	71	94.4	86.2–98.4
Parity	Nulliparous	63	93.7	84.5–98.2
	Multiparous	57	93.0	83.0–98.1
History of induced abortion	Yes	33	93.9	79.8–99.3
	No	87	93.1	85.6–97.4

Abbreviations: *N*, number of participants (full analysis set); 95% CI, Clopper–Pearson exact confidence interval.

misoprostol 48 h later.[7] However, it only reported an overall efficacy of 85.4% and an efficacy of 75% at 24 h after misoprostol administration.[7] Four large-scale randomized clinical trials showed that the mifepristone dose could be decreased to 200 mg without compromising efficacy.[15–18] Additionally, a recent systematic review of controlled trials evaluating the use of mifepristone (200 mg) followed by misoprostol for pregnancy termination at up to 63 days of gestational age and involving more than 45 000 participants revealed that the risk of abortion failure was higher when the total misoprostol dose was 400 μg, rather than a higher dose, and when misoprostol was administered orally, rather than vaginally, buccally, or sublingually.[6] Therefore, it is plausible that the difference in early efficacy between our study and others is attributable to the regimen itself.

A recent large Australian post-marketing study concluded that both the participants' age and gestational age had a significant effect on the success rate of medical abortion.[6,19] Contrarily, our study found no differences in correlation with the participants' age (94.4% in those aged ≤29 years vs. 91.7% in those aged ≥30 years) (Table 4). The only group showing a much lower efficacy than that

TABLE 5 Overall summary of AEs and ADRs (safety analysis set).

	Pre-treatment, *N* = 120	Treatment-emergent, *N* = 120	Post-treatment, *N* = 120	Total, *N* = 120
AEs/ADRs	**Event, *n* (%)**	**Event, *n* (%)**	**Event, *n* (%)**	**Event, *n* (%)**
Any AEs	7, 4 (3.3)	125, 69 (57.5)	1, 1 (0.8)	133, 71 (59.2)
AEs not related to IMPs	7, 4 (3.3)	58, 39 (32.5)	0, 0 (0.0)	65, 41 (34.2)
AEs related to IMPs (ADRs)	–	69, 45 (37.5)	1, 1 (0.8)	70, 45 (37.5)
Mild AEs	6, 3 (2.5)	92, 60 (50.0)	0, 0 (0.0)	98, 61 (50.8)
Moderate AEs	1, 1 (0.8)	29, 19 (15.8)	1, 1 (0.8)	31, 20 (16.7)
Severe AEs	0, 0 (0.0)	4, 3 (2.5)	0, 0 (0.0)	4, 3 (2.5)
Mild ADRs		55, 41 (34.2)	0, 0 (0.0)	55, 41 (34.2)
Moderate ADRs		13, 8 (6.7)	1, 1 (0.8)	14, 8 (6.7)
Severe ADRs		1, 1 (0.8)	0, 0 (0.0)	1, 1 (0.8)
Serious AEs	0, 0 (0.0)	6, 4 (3.3)	1, 1 (0.8)	7, 4 (3.3)
Serious ADRs		1, 1 (0.8)	1, 1 (0.8)	2, 1 (0.8)
AEs leading to death	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
AEs leading to treatment discontinuation	0, 0 (0.0)	0, 0 (0.0)	–	0, 0 (0.0)
AEs leading to trial discontinuation	0, 0 (0.0)	0, 0 (0.0)	–	0, 0 (0.0)

Note: AEs and serious AEs were described according to treatment administration, seriousness, severity, and relation to the IMPs.

Serious AEs were defined in all clinical studies as any untoward medical occurrence in the study participants that resulted in death; was life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; resulted in congenital abnormalities or defects; or were otherwise judged to be medically important events or reactions.

The severity of an AE was classified using a 3-point scale, as follows: (1) mild: awareness of signs or symptoms but no disruption of usual activity; (2) moderate: event significant enough to disturb usual activities; and (3) severe: inability to work or perform usual activities (unacceptable).

The safety analysis set included all participants who signed an informed consent form and received at least one IMP.

Abbreviations: AE, adverse event; ADR, adverse drug reaction; *N*, number of participants (safety analysis set); *n*, number of participants observed; %, percentage of participants.

observed in the Australian study was the group with a gestational age of <42 days, with a success rate of 83.3% (Table 4), which is contrary to our expectations.[19] A limitation of our study was the small sample size, which hindered robust interpretation for subgroup analyses.

The results of our rigorous safety evaluation during hospitalization are in agreement with the findings of previous studies in the literature[6–14,19]; serious and severe ADRs were rare, and the most frequently reported ADRs were mild-to-moderate gastrointestinal disorders. Additionally, this study provides details on abdominal pain and bleeding patterns during medical abortion. Bleeding sometimes lasted for several days; nevertheless, the heaviest bleeding usually occurred at around the time of GS expulsion. The mean pain score throughout the procedure was 5 on an 11-point NRS in this study. As the prophylactic use of analgesics during medical pregnancy termination could appropriately reduce and manage lower abdominal pain, they were also specified in our study protocol; 98.3% of the participants received analgesics. Reported pain can be significantly reduced when individuals have an understanding of what to expect before the procedure with respect to intensity and timing. Cavet et al. reported that the odds ratio for experiencing severe pain was 3.27 (95% CI: 1.09–9.74, $p = 0.0334$) in participants who did not receive any information, as compared with those who did.[20] Therefore, despite the different experiences among individuals, an understanding of what to expect in terms of intensity and timing is important for those undergoing the procedure.

While the regimen for medical abortion is already well established in an expanding number of countries, our study provides a detailed picture regarding the short-term success rate, as well as bleeding and pain patterns. This original evidence demonstrates that early medical abortion is a quick and safe process, allowing most participants to resume normal activities within one day. Furthermore, our findings suggest the absence of ethnic differences in efficacy or safety between the Japanese and other populations.

In conclusion, our study showed the excellent efficacy and safety profile of early medical abortion performed with a combined regimen of mifepristone and misoprostol. Medical abortion is expected to be a new available option in abortion care for individuals

TABLE 6 Serious treatment-emergent AEs (safety analysis set).

	N = 120
Serious treatment-emergent AE	***n*** **(%)**
Blood loss anemia	1 (0.8)[a]
Cytomegalovirus infection	1 (0.8)
Endometritis	1 (0.8)
Bacterial infection	1 (0.8)
Uterine hypotonus	1 (0.8)
Abnormal uterine bleeding[b]	1 (0.8)

Note: Events were encoded and tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 and translated into Japanese using MedDRA/J version 24.0.

[a]The participant experienced a moderate serious AE of "abortion induced incomplete" (reported term: residual placenta) during the post-treatment period.

[b]Metrorrhagia was encoded and tabulated using MedDRA version 22.0, was translated to "abnormal uterine bleeding" as preferred term (PT) using MedDRA/J version 24.0.

Abbreviations: AE, adverse event; *N*, number of participants (safety analysis set); *n*, number of participants observed; %, percentage of participants.

TABLE 7 Most common AEs and ADRs (observed in at least 2% of the participants) (safety analysis set).

	N = 120				
	Related to mifepristone	**Related to misoprostol**	**Related to mifepristone or misoprostol**	**Not related to either**	**Total**
	n **(%)**	***n*** **(%)**	***n*** **(%)**	***n*** **(%)**	***n*** **(%)**
AEs/ADRs	13 (10.8)	40 (33.3)	45 (37.5)	24 (20.0)	69 (57.5)
Anemia	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)	3 (2.5)
Abdominal pain lower	3 (2.5)	16 (13.3)	18 (15.0)	18 (15.0)	36 (30.0)
Vomiting	6 (5.0)	10 (8.3)	13 (10.8)	12 (10.0)	25 (20.8)
Diarrhea	1 (0.8)	17 (14.2)	17 (14.2)	0 (0.0)	17 (14.2)
Nausea	4 (3.3)	5 (4.2)	8 (6.7)	2 (1.7)	10 (8.3)
Pyrexia	0 (0.0)	3 (2.5)	3 (2.5)	1 (0.8)	4 (3.3)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)	3 (2.5)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)	3 (2.5)

Note: Events were encoded and tabulated using MedDRA version 22.0 and translated into Japanese using MedDRA/J version 24.0.

Abbreviations: AE, adverse event; ADR, adverse drug reaction; *N*, number of participants (safety analysis set); *n*, number of participants observed; %, percentage of participants.

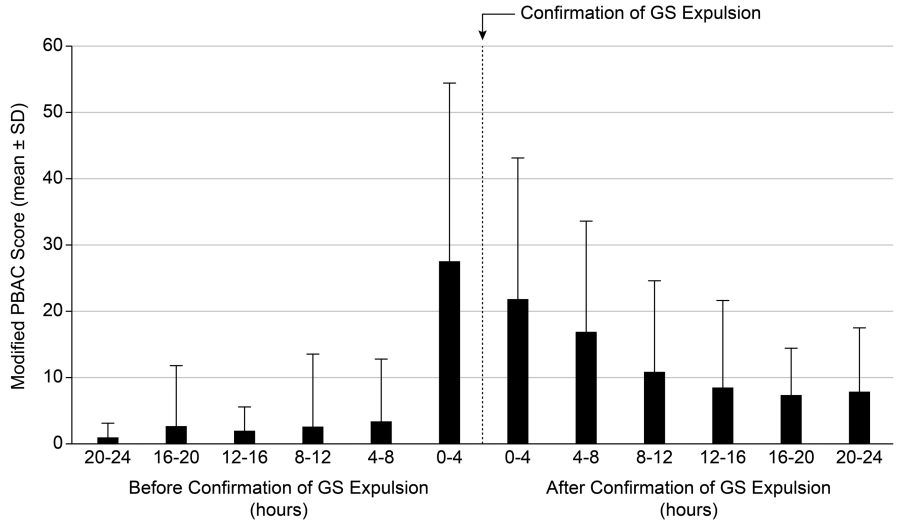


FIGURE 4 Time course of modified PBAC score before and after GS expulsion. Bleeding was tracked using the modified PBAC score. The mean (±SD) modified PBAC score was the highest 0–4 h prior to the confirmation of GS expulsion and then 0–4 h after the confirmation of GS expulsion; the modified PBAC score gradually decreased thereafter.

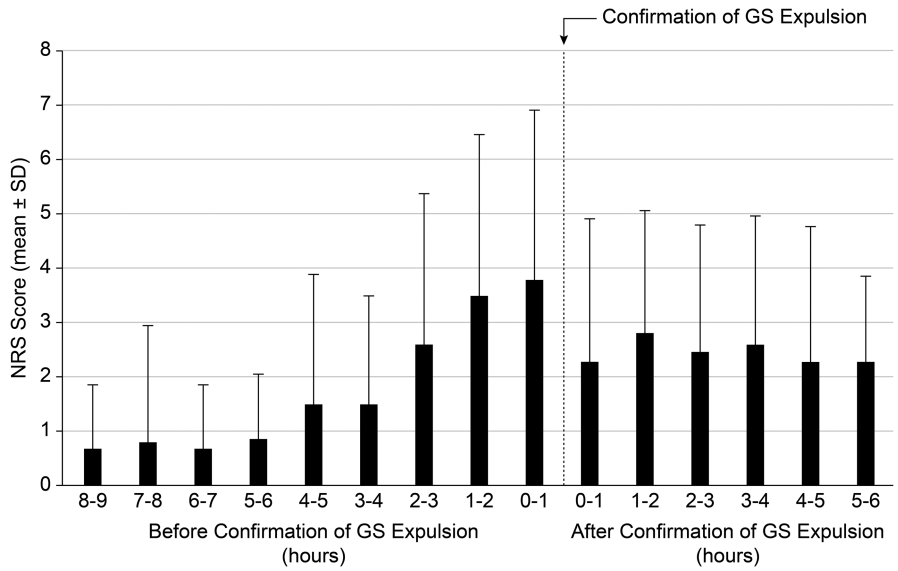


FIGURE 5 Time course of NRS score before and after GS expulsion. Lower abdominal pain was analyzed using the NRS. The most intense lower abdominal pain occurred 0–1 h before the confirmation of GS expulsion and then persisted at a consistent level until 3–4 h after the confirmation of GS expulsion.

seeking induced abortion as an alternative to traditional surgical abortion in Japan.

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CONFLICT OF INTEREST STATEMENT

The authors declare no Conflict of Interests for this article.

ETHICAL APPROVAL

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. This article does not contain any studies with animal subjects performed by the any of the authors. This study was reviewed and approved by five Institutional Review Boards (IRBs)—namely, (1) Maebashi Hirosegawa Clinic IRB (2-10-9 Chiyodamachi, Maebashi-shi, Gunma, Japan); (2) Yokohama Minoru Clinic IRB (1-13-8 Bessho Minami-ku, Yokohama, Kanagawa, Japan); (3) Shoda Hospital IRB (1-16-32 Annaka, Annaka-shi, Gunma, Japan); (4) Japan Conference of Clinical Research IRB (1-13-23 Minami-Ikebukuro, Toshima-ku, Tokyo, Japan); and (5) Review Board of Human Rights and Ethics for Clinical Studies (2-2-1 Kyobashi, Chuo-ku, Tokyo, Japan).

INFORMED CONSENT

Informed consent was obtained from all patients for being included in the study.

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